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THE THERAPEUTIC ROLE OF THE ESTROGENS*

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Natural Estrogens

The estrogenic hormone is one of the two ovarian hormones which has assumed considerable importance in clinical practice. Although the original source of this substance is the developing and mature follicle in the ovary, a number of metabolically changed substances are available from other sources such as blood and urine. All of these active principles obtained from natural sources have been designated as the natural estrogens. Thus we have available *estrone* or *theelin* derived from pregnancy urine; *estriol* or *theelol* derived from the same source, and *estradiol* first recovered from the ovaries of the sow. These natural estrogens all produce the same biologic effects but they vary considerably in potency. Thus, estradiol is the most effective and estrone the least effective. In the use of the natural estrogens it is important to take this variation in their potency into careful consideration. These three natural estrogens are available in pure form and in standardized preparations. They can be administered parenterally, orally, and by vaginal suppositories. Their effect varies with the preparation selected and the mode of administration. They are most effective on subcutaneous or intramuscular administration and least effective orally.

Synthetic Organic Estrogens

Since 1938, primarily as a result of the work of Dodds, Goldberg, Lawson and Robinson, we have available synthetic organic drugs with remarkable estrogenic properties. The best known of these synthetic organic estrogens are derived from

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the stilbene compounds. *Diethylstilbestrol* is one of some six substances that have been subjected to adequate trial. These organic estrogens have gained rapid popularity because they can be administered orally with as great effect as parenteral administration of the natural estrogens. They are inexpensive to use. Very careful observations over long periods of time do not reveal any differences in the biologic actions of the natural and synthetic estrogens so that they can be used interchangeably. For the past several years much of estrogenic therapy has been carried out with stilbestrol.

Estrogen Therapy Is Replacement Therapy

Estrogens should be used in those instances where the individual's own ovaries fail to produce the hormone or fail to provide an amount adequate for the needs of the individual. These estrogenic substances therefore should be used in the nature of replacement. When this fundamental principle of endocrine therapy is disregarded, the substance administered may lose its character of a hormone and assume that of a drug. Huge, unphysiologic amounts of estrogens have been administered with variable results, but these practices are not sound endocrinologic practice. In order to determine the proper therapeutic role for the estrogens we must review their normal physiologic roles.

Physiologic Considerations

Estrogens produced by the ovary are primarily growth-promoting principles. They reach a sufficiently high level at about puberty to initiate many of the changes which take place at this time (Fig. 15). Under their influence the secondary sex characters begin to differentiate and slowly attain their normal adult female appearance. The typical hair pattern of the lower abdomen and body develops. The breasts increase in size the estrogens promoting the growth of nipples, areolae and duct systems but having little effect on the secretory structures. The external genitalia develop to their normal state. The entire müllerian derivatives are under estrogenic control so that the vagina, uterus and fallopian tubes develop their adult state. The onset of cyclical activity

in the uterus is preceded by the growth of the endometrium as a result of estrogenic stimulation. Ultimately, when maturity is reached and ovulation occurs the endometrium is

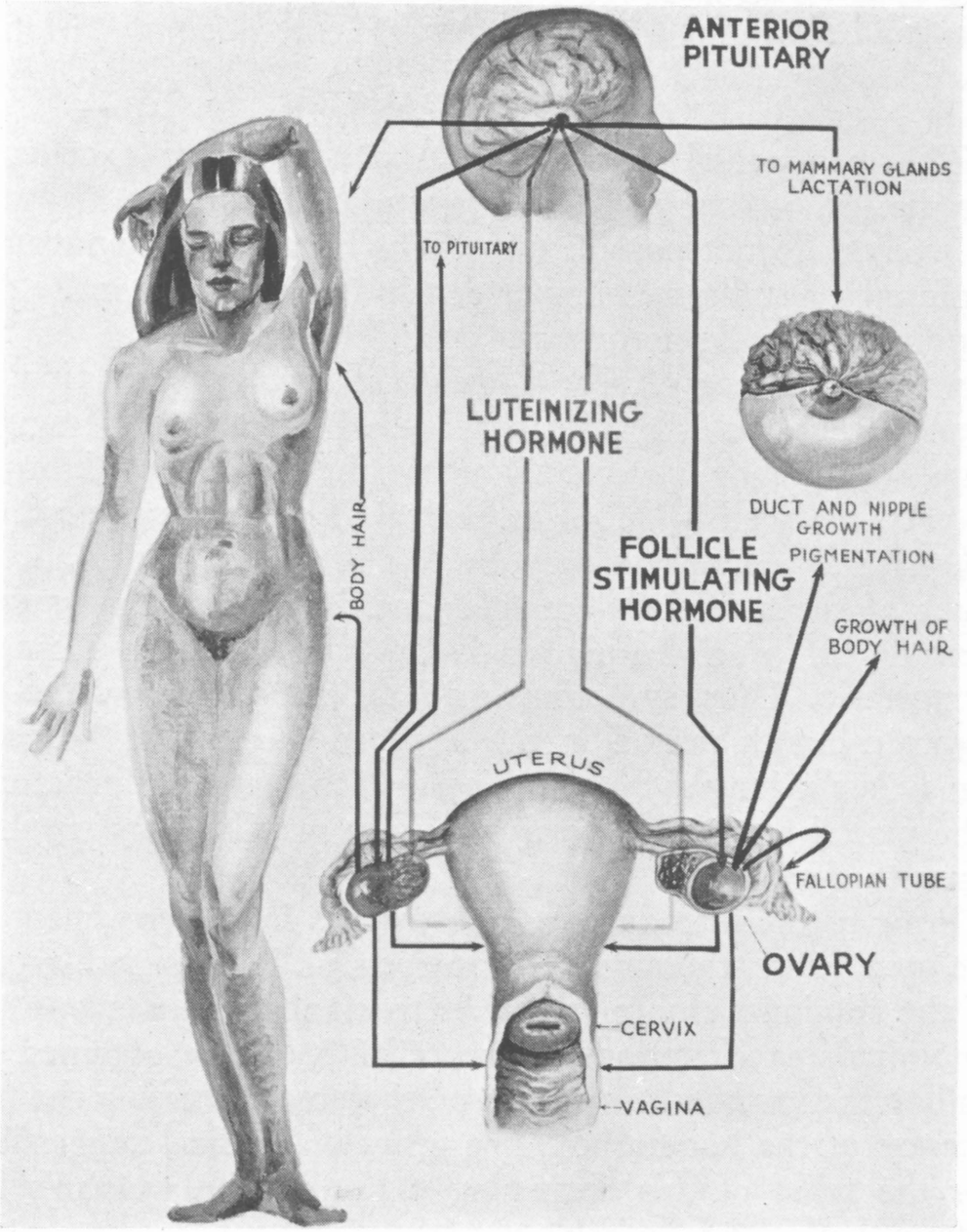

Fig. 15.—Physiologic role of the ovarian hormones and their pituitary control. The estrogenic or follicle-stimulating hormone controls cyclical changes in the entire reproductive tract, the ducts and nipples of the breast, pigmentation, the growth of body hair and epiphyseal closure.

converted into a functional phase by the appearance of progestin. Then periodically, during the entire reproductive period, estrogens promote the cyclical changes that take place

in the reproductive tract. Estrogens complete the osseous growth of the skeleton by inducing epiphyseal union. The therapeutic application of estrogens should retain their physiologic role as far as possible. Thus, their hormonal action can be maintained.

THE MENOPAUSE

The menopausal syndrome is a condition par excellence for the use of estrogenic medication. Although the majority of women do not consult physicians because of menopausal symptoms, a sufficient number demand treatment to make this condition a most important one. The physiology of the climacteric is not clearly understood, but the cessation of ovarian function brings in its wake a bizarre train of symptoms which may completely upset the normal equilibrium of even the well balanced individual. The insidious onset of the natural menopause may be less severe than the abrupt onset of the artificially induced one. However, the gradual cessation of ovarian function is likely to result in a longer climacteric. Thus, symptoms may extend over a twelve- to eighteen-month period in the artificial menopause, whereas it may last as long as five to six years in the natural climacteric. The period of waning ovarian activity may be very troublesome to the patient.

Prior to the introduction of estrogens in the treatment of the menopause, therapy was unsuccessful. It consisted largely of the administration of *sedatives* to combat the nervous and emotional manifestations. Some relief could be obtained by dulling the vasomotor mechanism, thereby decreasing the frequency of the hot flushes. The array of medical suggestions for the relief of this distressing period in the woman's life attests the lack of desirable results.

Estrogens were employed in the treatment of the menopause as substitution therapy. The extension of our knowledge in endocrinology soon made it apparent that the cessation of ovarian function was followed by an increased pituitary function, so that a follicle-stimulating gonadotropic substance appeared in the urine. Estrogens depress this gonadotropic function of the pituitary gland. There is a direct correlation

between the cessation of menopausal symptoms and the disappearance of gonadotropic substance in the urine (Fig. 16).

The early use of estrogenic substances for the treatment of the climacteric was not followed by uniformly good results. Indeed, competent investigators challenged its value and were inclined to credit the parenteral route of administration for much of its virtue. With the advent of crystalline natural estrogens which could be administered in larger amounts the results of therapy improved immeasurably. The dose of the

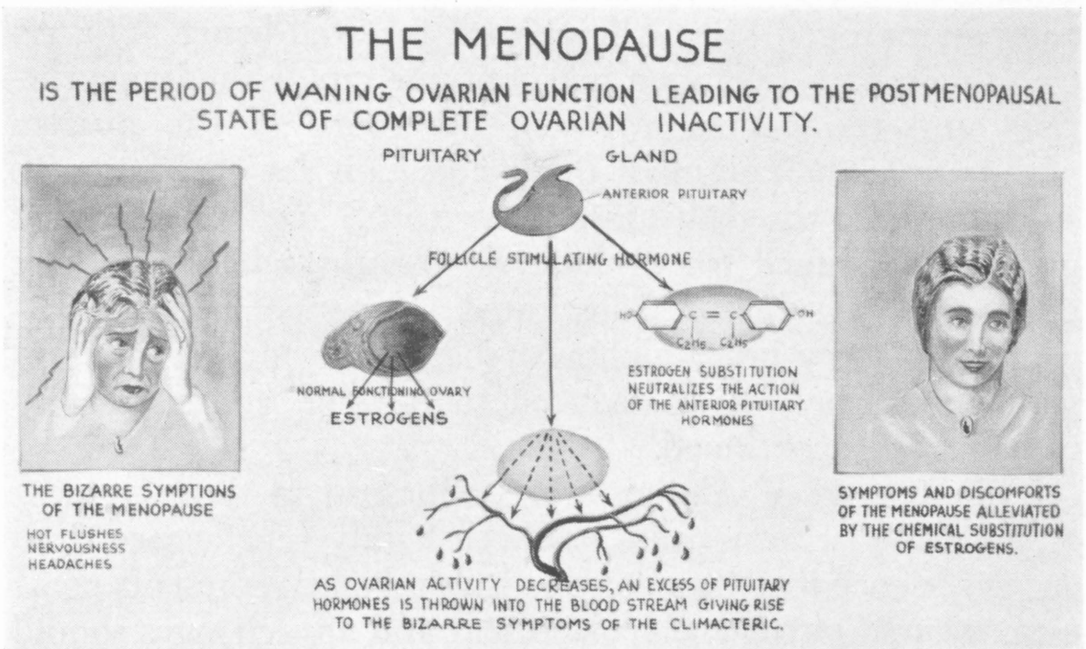
THE MENOPAUSE
IS THE PERIOD OF WANING OVARIAN FUNCTION LEADING TO THE POSTMENOPAUSAL STATE OF COMPLETE OVARIAN INACTIVITY.
PITUITARY GLAND
ANTERIOR PITUITARY
FOLLICLE STIMULATING HORMONE
NORMAL FUNCTIONING OVARY
ESTROGENS
ESTROGEN SUBSTITUTION NEUTRALIZES THE ACTION OF THE ANTERIOR PITUITARY HORMONES
THE BIZARRE SYMPTIONS OF THE MENOPAUSE
HOT FLUSHES
NERVOUSNESS
HEADACHES
SYMPTOMS AND DISCOMFORTS OF THE MENOPAUSE ALLEVIATED BY THE CHEMICAL SUBSTITUTION OF ESTROGENS.
AS OVARIAN ACTIVITY DECREASES, AN EXCESS OF PITUITARY HORMONES IS THROWN INTO THE BLOOD STREAM GIVING RISE TO THE BIZARRE SYMPTOMS OF THE CLIMACTERIC.

Fig. 16.—A diagrammatic presentation of the glandular mechanism responsible for the onset of the menopause and the role of estrogens in therapy.

natural estrogens necessary to control symptoms may vary from 30,000 to 100,000 I.U. per week.

The new synthetic drugs are ideal in the therapy of the menopause. *Stilbestrol* can be administered orally. A daily dose will provide a constant blood level of estrogenic principle more nearly replacing the natural estrogens. Apparently, 1 mg. a day is sufficient to alleviate all the hot flushes and most of the other menopausal symptoms. The hot flush is the only true menopausal symptom and its disappearance can be used as an indication of successful therapy. Nervous phenomena and headaches are less consistent end points.

Artificial Menopause

The artificial menopause has been treated with estrogens with excellent results. It may be well not to wait for the patient to develop ovarian withdrawal symptoms. We have treated many patients who have had no symptoms through their entire menopausal period. The administration of estrogens may be started ten days after castration by surgery or radiation of women during active reproductive years. The patient is given 1 mg. of stilbestrol each night just before bedtime. She should be cautioned to maintain a daily dose, for a constant estrogen level is important for well-being. The recovery from the operation will continue rapidly and uneventfully and the patient will not be aware of the ovarian withdrawal. She continues this medication for three months at which time the daily dose is cut to 0.5 mg. This amount may be continued for at least six months when a further cut to 0.25 mg. should be instituted, the patient taking a 0.5-mg. tablet every other night. At the end of another three to six months, the dose is reduced to 0.1 mg. and ultimately completely discontinued.

This method of administering stilbestrol in the treatment of the artificial menopause has been highly satisfactory. It is our experience that 1 mg. of the drug per day represents complete ovarian estrogenic replacement and any changes should be downward and not upward. If the patient's symptoms are menopausal in origin, 1 mg. per day will bring complete relief. The slow reduction in the daily amount allows for the gradual readjustment which must take place in the patient's endocrine system. It has been our experience that treatment of the artificial menopause may take from twelve to twenty-four months and that the average patient needs therapy for about eighteen months. It is well to discontinue treatment in the winter months when the return of an occasional hot flush is not troublesome.

Natural Menopause

The natural menopause is more difficult to treat because there may be a long period of failing ovarian activity. During these months, the patient menstruates irregularly and experi-

ences menopausal symptoms when the estrogens reach a low level. The uncertainty and marked fluctuations in the patient's own estrogens make accurate substitution difficult or impossible. Treatment should begin with small amounts, 0.1 to 0.5 mg. daily, and the effect on the hot flushes should be carefully observed. It is logical to administer the smallest amount necessary to keep all the hot flushes in abeyance. The amount of the drug may have to be increased slowly as the estrogenic function of the ovaries reaches a low ebb. Again, it has been our experience that no patient will require more than 1 mg. of stilbestrol per day. When complete substitution is reached, the amount may be slowly reduced, as previously described. The natural menopause may require from eighteen to thirty-six months and treatment has to be continued for an average of twenty-four months.

Precautions and Hazards

In spite of the fact that treatment of the menopause is highly successful in over 95 per cent of patients who need therapy, there are some precautions that must be taken and a few hazards to overcome.

In the first place, any patient who has *irregular bleeding* as part of the menopausal picture must be carefully examined to make certain that the bleeding is not a symptom of a serious underlying disease. In the absence of gross palpable findings, a diagnostic curettage is necessary to rule out an early carcinoma of the corpus of the uterus.

Estrogens occasionally *provoke bleeding*, thereby furthermore complicating the clinical picture (Fig. 17). The most common cause for bleeding during the administration of the drug is fluctuations in estrogen level produced by withdrawal of the drug. The continuity of the therapy must, therefore, be emphasized. Estrogen bleeding can occur on a constant estrogen level and is probably brought about by the proliferative changes in the endometrium. In the event of such bleeding it is well to discontinue medication for several weeks and longer. Bleeding should subside but, should it continue, a diagnostic curettage may be necessary.

About 12 per cent of patients experience some *nausea* at the

onset of therapy with estrogens. Natural and synthetic estrogens may provoke nausea if they are given in comparable amounts. In most patients the nausea will disappear in a few days if they continue to take the hormone. A rare individual,

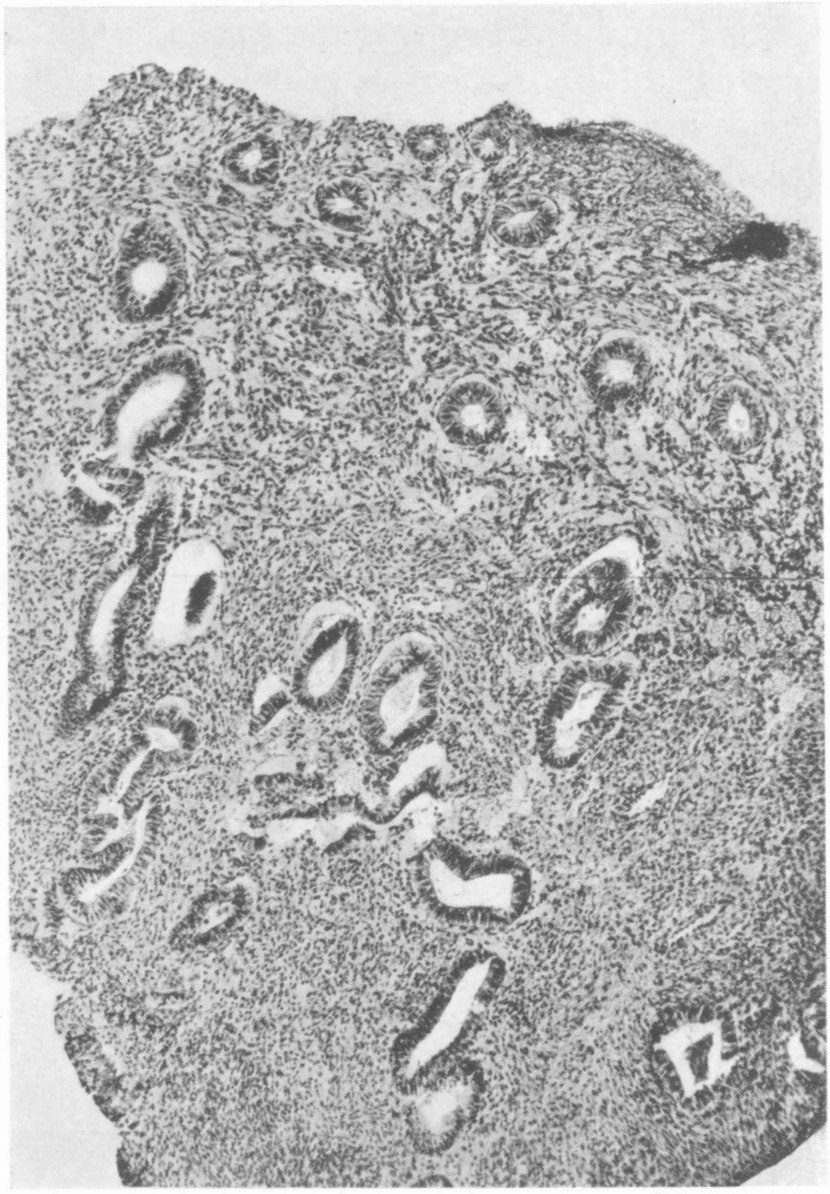

Fig. 17.—Biopsy of the endometrium obtained during a bleeding period. The mucosa undergoes moderate proliferation as a result of estrogenic stimulation but continued medication does not result in an increased change.

one or two in a hundred, cannot take any estrogenic substance even in minute amounts without serious nausea. There is no explanation for this interesting phenomenon.

No untoward symptoms or findings have been observed in well over 1000 patients who have been most carefully ob-

served during the last four years. In some experimental animals estrogens are carcinogenic. However, there is no good evidence that they exert similar properties in the human. The possibility of producing a cancer by their administration in clinical amounts can be regarded as highly improbable.

POSTMENOPAUSAL VAGINITIS

Davis in 1935 first demonstrated the value of estrogens in the treatment of postmenopausal vaginitis. The development of the vaginitis follows an inflammation superimposed upon the atrophic mucosa. The exciting agent may be some minor trauma which injures the thin, inactive squamous epithelium. The patient develops a sensation of burning or itching, dysuria and frequency and a serosanguineous or gluey discharge. These symptoms are exceedingly troublesome and annoying. Estrogens rapidly convert the atrophic squamous epithelium into the normal active mucosa of middle life (Fig. 18). These cellular changes result in a rapid disappearance of the inflammation beneath the mucosa and the establishment of a normal biologic flora. The pathogenic organisms disappear and all symptoms subside. At the cessation of therapy, regressive changes set in and the mucosa of the vagina slowly reverts to its previous state. However, symptoms of vaginitis will not reappear unless trauma and infection recur.

Estrogens are administered in a small vaginal suppository. Usually 0.5 mg. of stilbestrol is used each night for six to eight weeks. The simplicity of this therapy, the immediate and complete relief provided the patient, and the absence of untoward effects make this management ideal.

INHIBITION OF BREAST ENGORGEMENT

It is occasionally desirable to prevent engorgement and lactation following delivery, as when the child is stillborn. In other instances the nipples may be so poorly developed that nursing would be impossible. The patient may have had a breast abscess in a previous puerperium and it may be well not to try nursing a second time. Maternal conditions such as tuberculosis or heart disease may make nursing undesirable.

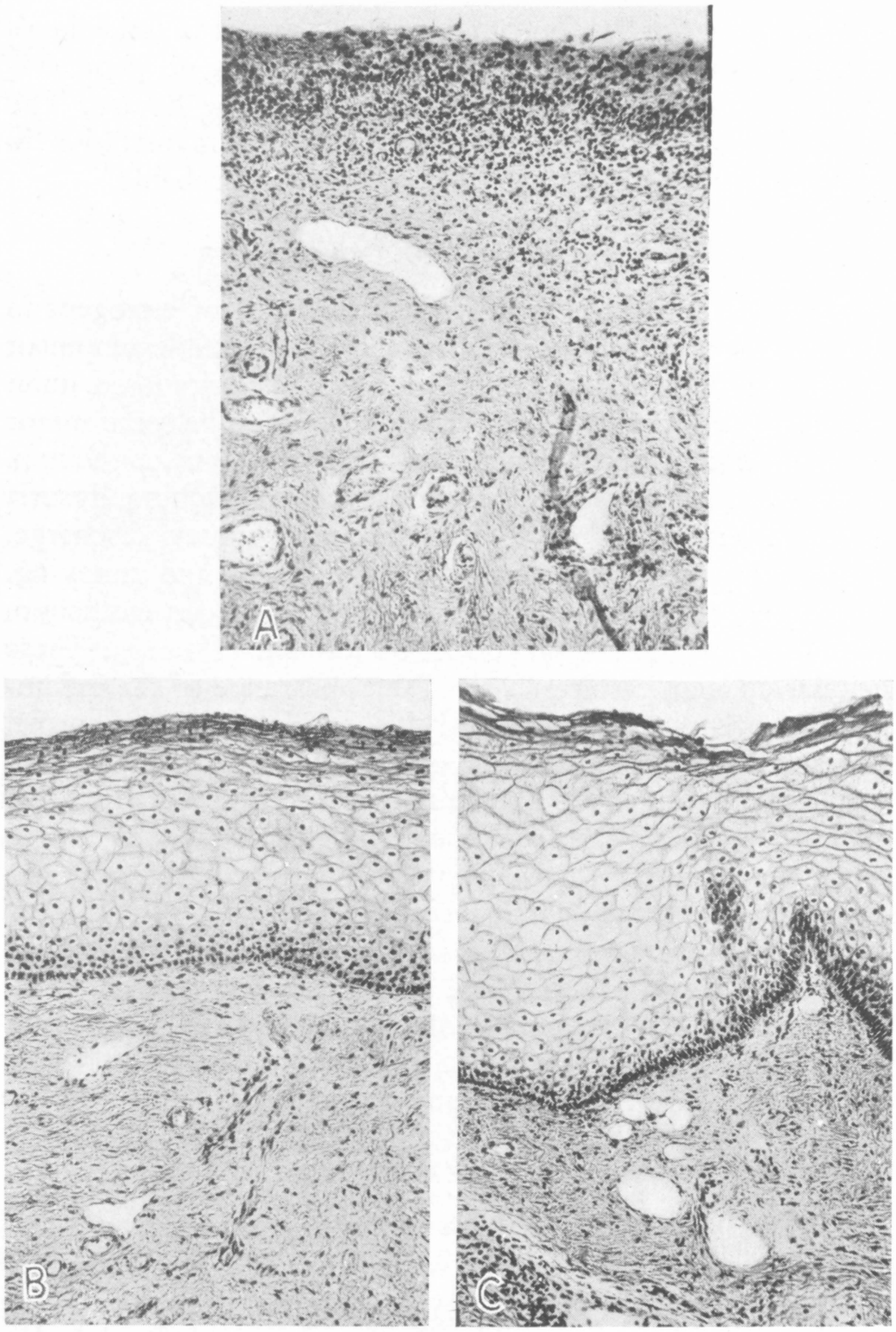

Fig. 18.—Biopsies of the vaginal mucosa in a patient with postmenopausal vaginitis before and after therapy with estrogenic suppositories. (All photomicrographs were magnified 42.5 times for accurate comparison.)

A, Before therapy. The squamous epithelium consists of four or five layers of cells which are small and indistinct. The basal layer of cells is

It is possible to prevent all breast discomfort in all of these circumstances by the administration of an estrogenic drug. If it is administered sufficiently early in the puerperium, no engorgement or lactation will take place. The usual practice is to give the patient a 5-mg. tablet of diethylstilbestrol immediately after delivery and each day for seven or eight days. No binders or breast care is necessary.

In the event that nursing has commenced and has been maintained for some days or weeks, stilbestrol is no less effective. The breasts return to their normal state within forty-eight hours after the beginning of therapy. No binder, ice cap or limitation of fluid is necessary. In a small group of patients a very slight secretion of milk will recur after the cessation of treatment. This recurrence is neither troublesome nor does it demand treatment.

PRIMARY AMENORRHEA

The onset of menstruation or puberty heralds the advent of adolescence and sexual maturity. Normal physical feminine development and the capacity for reproduction depend on normal reproductive organs which function as a result of a closely correlated endocrinal relationship. In some young women menstruation fails to take place. Although this failure is only one manifestation of an abnormal reproductive mechanism, it provides the name of primary amenorrhea.

The absence of the menses in a young woman may be the result of a lack of normal development of all or a part of the

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somewhat irregular. There is no sharp demarcation between the cells and the subepithelial zone. No mitotic figures can be seen. A moderate infiltration of round cells and a few polymorphonuclear leukocytes can be seen in the subepithelial zone, indicative of the inflammatory condition.

B, Four weeks after the daily administration of a 0.5-mg. stilbestrol suppository vaginally. Note the complete restoration of the squamous epithelium to that seen during active sex life. The basal cells are arranged regularly and show signs of cellular activity. All of the cells are large, clear, sharply demarcated, and contain an abundance of glycogen. The functionalis is beginning to develop. Note the increased vascularity of the subepithelial connective tissue and the complete disappearance of inflammatory cells.

C, Eight weeks after the onset of treatment. Note the increasing thickness of the squamous epithelium. The functionalis has been completely restored. The active basal cells comprise several layers.

reproductive tract. The uterus may be underdeveloped or rudimentary, or its canal may be nonpatent. The vagina may be absent or its lumen may fail to provide continuity with the uterus. The gonads may be absent or abnormal. The menstrual function may be absent because of an endocrinal failure, pituitary or ovarian in origin. The anterior lobe of the pituitary provides the motor for the cyclical changes which take place in the reproductive organs. Pathologic conditions in the pituitary gland may hold these changes in abeyance or completely inhibit them. The ovaries may not be responsive to normal pituitary stimuli because of abnormal development, thereby resulting in uterine inactivity. While it often is possible to determine which of these factors operate in a woman with primary amenorrhea, it may or may not be possible to correct or remove the cause.

A lack of normal development of the sex function may have a profound effect on the physical, psychic and even mental development of the young woman. In some of these persons puberty and the changes it initiates are delayed into adulthood. Thus the bony skeleton may fail to develop normally as a result of delayed epiphyseal closures, secondary sex characters which differentiate the woman from the sexless child may all be absent, and the normal feminine figure fails to evolve. Associated with this lack of physical development, there usually occurs a retarded psychic development which results in an abnormal social adjustment. The young woman may begin to brood over her physical and sexual inequalities. She magnifies their importance to such an extent that she develops an inferiority complex, a temporary or permanent psychosis, or abnormal sex relationships. Menstruation, therefore, although only one index of functioning reproductive organs, becomes of paramount importance to these young women with primary amenorrhea.

Obviously, in the presence of only rudimentary portions of the müllerian derivatives or in their complete absence, vaginal bleeding is impossible. On the other hand, when a lack of normal development of these organs is present or an abnormal endocrinal relationship interferes with normal sex activity, improvement and perhaps a restoration to the normal

is, theoretically at least, possible. Every advance in endocrinology has offered one more challenge to find a solution to some of these interesting problems.

Theoretically at least, in many of the patients with primary amenorrhea, *gonadotropic substances* which supplant the action of the normal anterior lobe of the pituitary gland should prove efficacious. These gonadotropins should stimulate the ovaries to normal cyclical activity so that these structures can produce the hormones necessary for endometrial growth, secretion and menstruation. It has been found, however, that impure gonadotropic substances from pregnancy urine and from gland extracts have little effect on the human ovary. Equine gonadotropin more nearly reproduces the action of the normal pituitary gland and is the most potent of our gonadotropic principles. Some results have been obtained with pregnant mare serum in the treatment of primary amenorrhea, but in the majority of instances the treatment has been unsuccessful. It is possible that the ovaries of these women are primarily at fault. Their ovaries may be so abnormal or undifferentiated that they are refractory to stimulation by the pituitary gland, in which event gonadotropic therapy is doomed to failure.

The administration of estrogens must be considered as purely substitution therapy. The *natural estrogens* can bring about the development of the reproductive organs, the breasts and the secondary sex characters. To accomplish this, however, estrogens must be administered in comparatively huge doses intramuscularly, and at frequent intervals, to maintain a constant level of blood estrogens. On the withdrawal of this hormone, regressive changes begin, so that after a short time the structures revert to almost their previous state.

Stilbestrol has provided an ideal estrogen for the treatment of this condition. The daily oral administration of a small amount provides a sufficient estrogenic stimulus to produce physical and sexual maturity of these underdeveloped young women. The changes induced in these patients in a short period of a month or more are truly astounding.

The following case history is typical of the group of young women with primary amenorrhea.

S. B., now twenty-four years of age, had never menstruated when she came to our clinic in 1936 at the age of eighteen years. She had been treated elsewhere for her amenorrhea since 1934. At eleven years of age a scanty growth of pubic and axillary hair

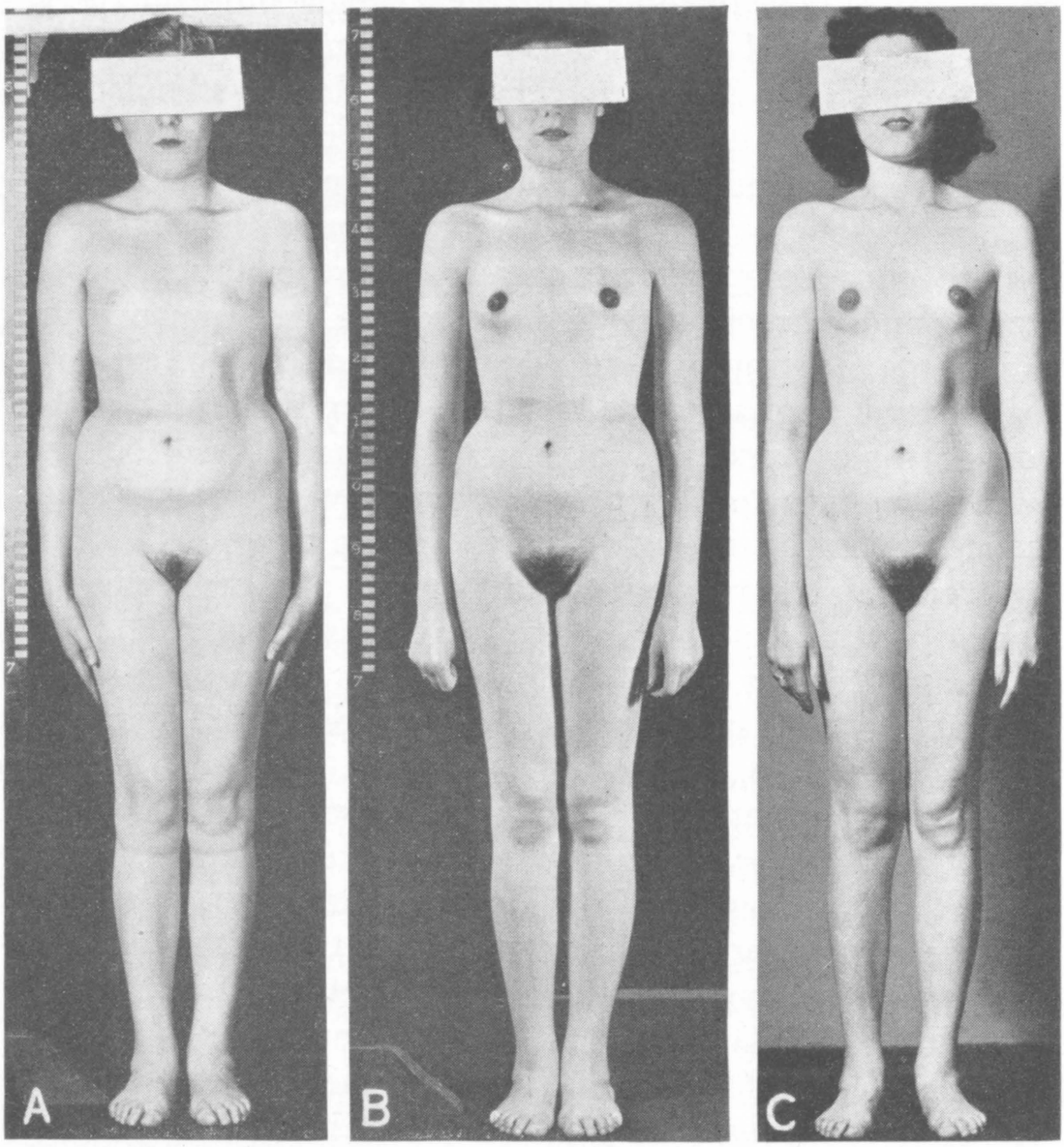

Fig. 19.—*A*, S. B., before the onset of therapy. *B*, After six months of estrogenic therapy. Note the bodily development, the feminine hirsuties, the development of the breasts. *C*, After three years of estrogenic treatment. Note the normal mature figure and the normal development of the secondary sex characters.

had appeared, but no further secondary sexual development occurred and she retained the square shoulders, narrow and boxlike hips and juvenile facies of the prepubertal girl.

When first seen by us in 1936 her appearance was typically pre-

adolescent. There were practically no breasts and the pale areolae measured only 8 mm. in diameter. Tiny, flat nipples resembled those of a six-year-old child. The pubic and axillary hair was

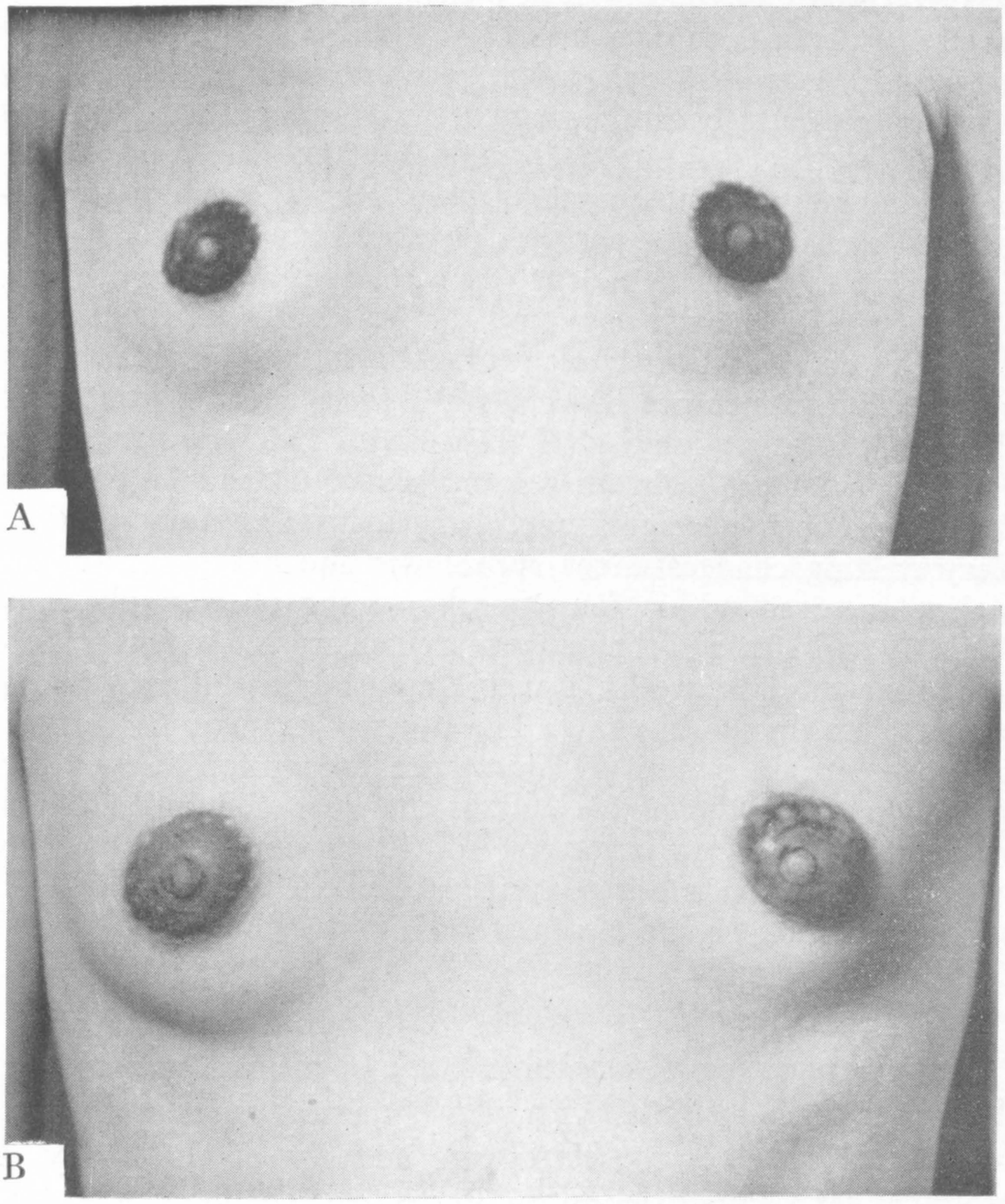

Fig. 20.—*A*, Breast development after six months' substitution therapy with estrogens. The breast development is largely growth of the duct system, the areolae and the nipples. The pigmentation of the areolae is striking. *B*, Breast changes after three years of substitution therapy. The appearance of the breasts has not changed after the first year of therapy. The striking changes resemble those seen in pregnancy.

thin and sparse; the labia were almost nonexistent, and the vagina which admitted a finger tip with difficulty was narrow, short and smooth-walled. The uterus was small and consisted mostly of

cervix. No adnexa could be palpated. Basal metabolic rates ranged between minus 9 and minus 17 per cent. The visual fields were normal. X-ray studies revealed normal epiphyses with delayed closure in the proximal phalanges. There was no abnormality of the sella turcica.

From 1936 to 1938 the patient received mainly gonadotropic preparations, latterly supplemented by parenteral administration of natural estrogen in single doses of 20,000 to 100,000 I.U. preceding courses of equine gonadotropin. No vaginal bleeding and very little change in the patient's physical state occurred.

On May 1, 1939, the patient was placed on a dosage of 1 mg. of stilbestrol by mouth daily and she has continued this routine dose with occasional brief rest periods to the present time. There has been no intolerance. Except for a sharp and permanent increase in the hemoglobin level from 8.8 to 13.8 gm. per 100 cc. of blood, with cell volumes respectively of 25 and 41 per cent, there have been no significant changes in laboratory findings. Very striking changes in the appearance and personality of this patient occurred within four months, as the photographs show (Figs. 19 and 20), and the patient has menstruated at intervals of from four to eight weeks, usually requiring withdrawal of the stilbestrol to invoke bleeding. The breasts and external genitalia are now entirely normal in appearance except for marked pigmentation about the nipple and in the linea abdominalis. This pigmentation is of great interest and its significance and mechanism of formation is being investigated at the present time. The patient's outlook on life has improved immeasurably.

Comment

Many interesting observations have been made concerning the treatment of patients with primary amenorrhea. Stilbestrol completely replaces the estrogenic activity of the ovary. It produces sexual maturity in the immature female with the exception of ovarian function. The prepubertal state is rapidly replaced by the physical and organic development of the mature woman. All of the secondary sex characters develop. The reproductive organs assume the normal adult type. The undifferentiated juvenile physical characteristics give way to the mature feminine form. The speed of the transition is remarkable, for all this is accomplished in a period of several months, whereas normal adolescence requires three or four

years. The gonads are the only reproductive organs that are not affected and remain dormant.

It was possible to produce some of these changes by means of the natural estrogens when they were administered at frequent intervals and in large doses. It has not been possible, however, with the natural estrogens to produce the degree of physical and sex development seen in women with primary amenorrhea who were treated with stilbestrol. Furthermore, it has been impossible with the natural estrogens to maintain the development for long periods of time so that the patient would be benefited by the change. The natural estrogens were administered intramuscularly at varying intervals and for short periods of time. This mode of medication probably resulted in varying concentrations of blood estrogens not conducive to optimum results. On the other hand, oral medication can be easily maintained over long periods of time, thereby producing a constant estrogen level in the blood and tissues.

Obviously, this substitution therapy must continue in order that these young women remain normal. When natural estrogens only were available, continued therapy was impossible and undesirable. Now that it is possible to take a small tablet of stilbestrol once a day or less often, prolonged substitution becomes entirely feasible. There can be no question as to the desirability of continued therapy in these young women, provided this therapy is safe and no injurious effects occur. Only careful clinical observations and experimental studies over long periods of time will answer these questions. No one doubts the wisdom of continued substitution therapy in hypothyroidism, in diabetes, and in other glandular deficiencies. Why should one doubt the wisdom of continued therapy in hypo-ovarianism?

The *amount* of stilbestrol necessary to maintain the optimum development of the individual is difficult to ascertain. Larger amounts of the drug are necessary during the transitional period, but small amounts may suffice to retain the desired changes. About 0.5 mg. daily has been sufficient to prevent any regression, and it is entirely possible that this amount is too large. Careful endocrinal assays may reveal the

optimum daily consumption of this drug. Nature is very lavish in the production of its own endocrines and much of the excess is destroyed or eliminated. Substitution therapy need not be that extravagant.

Periods of bleeding occur seven to twenty days following the sudden withdrawal of the drug as well as on continued medication. These periodic bleedings occur with some degree of regularity. The only difference between true ovulatory menstruation and these anovulatory bleedings is in the *endometrial picture*. The mucosa of the uterus develops a moderate proliferative phase, but continued medication with stilbestrol does not result in continued proliferation of the endometrium. The endometrial picture resembles that normally encountered prior to ovulation. The bleeding is preceded by the usual premenstrual prodromas, and subjectively these periods are very much like normal menses. The blood loss is scant in amount and there is no loss of desquamated endometrial fragments. The character of these periodic bleedings provides additional evidence as to the fundamental physiologic mechanisms underlying normal menstruation.

The development of the *breasts* is limited to a growth of the duct system. No changes take place in the secretory acini, for these are not stimulated by the estrogens. The nipples and the areolae show pronounced growth changes. No secretion is present in these breasts.

The *pigmentation* that occurs is most marked in the nipples and the areolae, but the linea alba as well as other mildly pigmented areas become intensely discolored. As the treatment is continued, the pigmentation of these areas increases in intensity. This unusual pigment response is much greater in degree than that usually seen in normal pregnancy. The natural estrogens provoke pigmentation, but not in the degree seen in these patients. We are conducting studies into the nature of this pigmentation.

DYSMENORRHEA

In a small group of patients, painful menstruation may be the result of an underdevelopment of the reproductive organs. The uterus may be small and have infantile characteristics.

Theoretically, estrogens, by promoting the development of the uterus, should improve the dysmenorrhea. This probably occurs in some instances. However, the use of estrogens for the relief of menstrual pain has been highly disappointing. In addition, the hormone may disrupt the normal cycle.

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